REMARKS

According to the Advisory Action dated April 18, 2005, the Amendment and Response to the Office Action of December 15, 2004 made under 37 CFR § 1.116 and dated March 15, 2005, was not entered into the file.

The current paper provides a second response to the issues raised in the Office Action, and makes no amendments. The remarks below explain why the application is already in condition for allowance, which is respectfully requested.

Claims 13-40 are pending in the application, and stand variously rejected. The rejection has been made final. Reconsideration and allowance of the application is respectfully requested.

Interview

The undersigned is grateful to Examiner Thái-An N. Ton and Examiner Joseph Woitach for the courtesy of several interviews at the Patent Office on March 2, 2005, regarding this and other applications relating to human pluripotent stem cells.

The remarks presented here were discussed at the interview. The application is believed to be in condition for allowance, which is respectfully requested.

Double Patenting

The pending claims stand provisionally rejected for obviousness-type double patenting over certain claims of copending application USSN 10/087,142.

The prosecution of the present application is more advanced than the 10/087,142 application. Accordingly, it is expected that the present application will issue as a U.S. Patent first, and no terminal disclaimer is required.

The pending claims also stand rejected for obviousness-type double patenting over claims 1-3 of U.S. Patent 6,458,589. The Office Action indicates that the claims in the present application are obvious because the cell populations of the '589 patent have the same characteristics as cells produced by the methods of the instant claims.

Applicant respectfully disagrees. Even if the Office is entitled to use a one-way test in this instance, applicant submits that the test has been applied *backwards*. The question is not whether the claims in the issued patent are obvious with respect to the claims here, but the opposite — whether the

method claimed here is obvious with respect to the *product* claimed in the issued patent. The test is applied to the claims alone, without regard to what is taught in the specification. MPEP § 804 (II)(B)(1)(a).

On this basis, the doctrine of obviousness-type double patenting does not apply. The methods claimed here explicitly require the use of a *histone deacetylase inhibitor* as an *ingredient* in the method. The use of this ingredient is not taught or suggested in the *claims* of the issued patent.

Withdrawal of this rejection is respectfully requested.

Rejection under 35 USC § 112

Applicant acknowledges with gratitude that the previous enablement rejection for differentiation of the pPS cells before use of the histone deacetylase inhibitor, as an optional step, has been removed.

The pending claims now stand rejected under 35 USC § 112 ¶ 1 as not being enabled for making hepatocytes from pPS cells with histone deacetylase inhibitors other than 5 mM butyrate. The Office Action refers again to the article by Lee et al. (Genesis 38:32, 2004) as teaching that the effect of butyrate on embryonic stem cell differentiation is dose-dependent.

Applicant respectfully disagrees. It is unnecessary for the claims to indicate the concentration of butyrate needed to effect differentiation into hepatocyte lineage cells. The specification exemplifies butyrate concentrations that are effective. Should the reader decide to deviate from the exemplified concentration, this can be done without undue experimentation — the protocol is just repeated with the altered butyrate concentration, and the cell culture is monitored for the presence of hepatocyte lineage cells having the characteristics required by the claim. Thus, a full working range of effective concentrations can easily be determined without undue experimentation.

By the same process, the skilled reader can determine as a matter of routine experimentation what other histone deacetylase inhibitors are effective in making hepatocyte lineage cells from pPS cells, and what an optimum concentration would be. As a further illustration, Table 7 in the working examples shows that propionic acid, isovaleric acid, isobutyric acid, and Trichlostatin A are all suitable for driving hepatocyte differentiation of pPS cells. Table 8 shows that Trichlostatin A induces hepatocyte phenotype to the level of 41%, 81%, >70%, and >90%, based on expression of albumin, α_1-antitrypsin, CK18, and CK19 respectively. The most extensively studied histone deacetylase inhibitor in the working examples was butyrate. The skilled reader would understand that given time to optimize use of propionic acid, isovaleric acid, isobutyric acid, Trichlostatin A, and other suitable

histone deacetylase inhibitors, the level of hepatocyte markers produced would also be optimized in respective protocols.

Applicant respectfully submits that the Office has not set forth sufficient basis for rejecting the claimed invention under § 112 ¶ 1.

In order to make a rejection for lack of enablement, the Office has the initial burden to establish a reasonable basis to question the enablement of the claimed invention.

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure *and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. In re Marzocchi,* 169 USPQ 367, 370 (CCPA 1971), italics added.

According to the legal standard, applicants don't even need to provide a single working example to comply with the patentability requirements of § 112 ¶ 1. *Gould v. Quigg* 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987).

Where a single illustrative example is provided, Federal Circuit case law clearly establishes that a patent applicant is not required to limit coverage to the working examples. Broader coverage is available under § 112 ¶ 1, providing there is no prior art that encroaches on the claimed scope outside the working examples.

By way of illustration, the patent application at issue in the case *In re Herschler,* 200 USPQ 711 (CCPA 1979) disclosed a method using a particular corticosteroid in DMSO. This was considered sufficient to support claims drawn more generally to a method of using a mixture of a "physiologically active steroid" and DMSO.

> The presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered . . . To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims. MPEP § 2164.02.

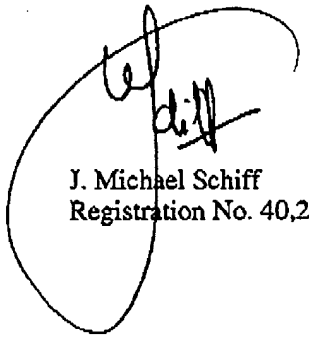
Applicant respectfully submits that the evidence in the disclosure showing the effectiveness of butyrate in a number of experiments, and the effectiveness of four other compounds (including Trichlostatin A) in initial testing, enables the skilled reader to identify and optimize other histone deacetylase inhibitors without undue experimentation, within the standards required by the case law.

Withdrawal of this rejection is requested.

The applicaton is believed to be in condition for allowance, which is hereby requested.

The fee for the extension of time is provided with the accompanying documents. No other fee is believed due for entry or consideration of this Amendment. Nevertheless, should the Patent Office determine that an extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief, and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,



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